

One Year of Lamivudine Therapy for Portuguese Patients with Chronic Hepatitis B

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Abstract

Objective: To assess the efficacy of lamivudine treatment on hepatitis B e antigen (HBeAg) and/or hepatitis B surface antigen (HBsAg) seroconversion, on other virological and serological markers of response including hepatitis B virus (HBV) DNA and serum aminotransferases, and the safety of lamivudine treatment in hepatitis B patients.

Patients: This phase III open-label study evaluated the virological and biochemical response to lamivudine in 70 Portuguese patients with HBeAg positive chronic hepatitis B. Patients were treated with lamivudine 100mg once daily for 12 months.

Methods: Antiviral activity was assessed by measuring alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels at all protocol visits, and hepatitis B serology and HBV DNA were performed at baseline and at month 12 visits. Evaluation of safety and tolerance was based on clinical adverse events and laboratory analyses.

Results: The primary endpoint was virological response at month 12, defined as loss of detectable HBeAg from serum with a reduction of HBV DNA to undetectable levels, and this was observed in 19/69 (27.5%) of patients. Almost half of the patients were HBV DNA negative by this time. Mean ALT values decreased steadily during treatment and by 12 months 61% of patients had values within the normal range. HBeAg seroconversion (HBeAg negative, HBeAb positive) was achieved in 27.9% of patients by 12 months, although all patients remained HBsAg positive.

Conclusion: Lamivudine was well tolerated and the incidence of adverse events was similar to those reported in previous studies. Lamivudine treatment resulted in virological and biochemical improvements in HBeAg positive chronic hepatitis B patients, with HBeAg seroconversion in one-third of patients.

Hepatitis B virus (HBV) infection constitutes a major global health problem. Estimates for the year 2000 by the WHO were for 400 million people worldwide to be chronically infected with HBV.^[1] Chronic HBV carriers with evidence of active HBV replication are at highest risk for the development of progressive liver disease.^[2,3] Approximately half of adult HBV carriers have evidence of viral replication, and in this group 15–20% may develop cirrhosis within 5 years.^[4–7] For patients with HBV-associated chronic hepatitis and cirrhosis, 5-year survival rates as low as 55% have been reported; for patients with cirrhosis and signs of hepatic insufficiency, 5-year survival may be as low as 14%.^[2,8] In addition, there is a significantly increased incidence of hepatocellular carcinoma in patients with chronic hepatitis B (CHB).^[9]

The goal of antiviral therapy for HBV infection is to reduce the risk of progressive liver disease by providing long-term suppression or eradication of HBV infection. Lamivudine is the first oral antiviral therapy approved for the treatment of CHB. Lamivudine is a nucleoside analogue that rapidly

and profoundly suppresses hepatitis B virus replication through inhibition of viral DNA synthesis. Previous studies have shown that, for patients with CHB, 1 year of lamivudine therapy resulted in persistent suppression of HBV DNA, and a significantly enhanced hepatitis B e antigen (HBeAg) seroconversion rate with significant reductions in necroinflammatory activity and delayed progression of fibrosis compared with placebo.^[10–13] Lamivudine treatment was also associated with a significant reduction in progression to cirrhosis compared with placebo.^[9] The aim of the current study was to assess the efficacy (HBeAg and hepatitis B surface antigen [HBsAg] seroconversion and other serological markers of response) and safety of lamivudine 100mg taken once daily for 1 year in 70 Portuguese patients with chronic hepatitis B.

Patients and Methods

Study Participants

Patients eligible for enrolment into this open-label study included males and females 16–70 years

of age with detectable HBsAg and HBeAg in serum at the time of screening and detectable HBsAg for at least the previous 6 months, detectable serum HBV DNA levels (DNA enzyme immunoassay detection system, DiaSorin, Vercelli, Italy) and alanine aminotransferase (ALT) levels of between 1.3 and 10 times the upper limit of the normal reference range (ULN) at screening. Patients were excluded if they had hepatitis C or D or HIV infection; decompensated liver disease (defined by a serum bilirubin level more than 2.5 times ULN, a prothrombin time prolonged by more than 3 seconds, and a serum albumin level lower than the normal reference range or a history of ascites, variceal haemorrhage or hepatic encephalopathy); or evidence of autoimmune hepatitis. Patients were also excluded if they had received an investigational drug within 30 days before enrolment, or were known to require any systemic antiviral therapy, immunomodulators, cytotoxic agents or corticosteroids. Pregnant and lactating females were excluded.

All patients provided written informed consent before participating in the study.

Study Design and Evaluations

The study protocol was approved by Ethics Committees at each of the institutions involved, and was performed at 22 investigational centres in Portugal according to the latest version of the Declaration of Helsinki. Patients received open-label lamivudine 100mg once daily for 52 weeks. No interim analyses were performed.

The screening visit was carried out within 4 weeks of the baseline visit, at which study medication was dispensed. After the baseline visit, patients returned every 3 months up to month 12, for assessment. At the screening visit and at month 12 (or after withdrawal from the study), serum was assayed for HBV DNA (DNA enzyme immunoassay detection system – limit of detection: 1000 copies), HBsAg and anti-HBs if HBsAg was undetectable (Chemiluminiscens, Diagnostic Product Corporation, Los Angeles, CA, USA), HBeAg and anti-HBe (ELFA Enzyme Linked Fluorescent Assay, Biomerieux Marcy, l'Etoile, France) by a single

laboratory (Endoclab, Laboratorio de Endocrinologia e Patologia Clinica, Porto, Portugal). At each visit, a physical examination was carried out and routine haematological and biochemical assays were performed to determine the safety of the treatment. Adverse events that had occurred since the previous visit were also recorded. The study was not designed to evaluate compliance with study medication. Virological testing for YMDD variant was not included in the protocol.

The study design was as similar to routine standard clinical practice as possible, therefore there were no specific requirements for liver biopsies; however, prior biopsy results could be recorded. The disease stage was assessed as follows; (i) inflammation/activity graded as none, mild, moderate or severe; (ii) fibrosis (disease stage) evaluated as none, mild, moderate or severe. Presence or absence of cirrhosis was also indicated. No specific scale system was used, as these were the results of patient biopsies performed prior to study entry. No post-treatment biopsies were required by the protocol.

Data Analysis

All patients were receiving open-label treatment, and since there were no planned treatment comparisons, only descriptive statistics are presented for the efficacy data. For the analysis of biochemical and virological response, patients with missing data were included and treated as having no response. For the analysis of median values of liver enzymes, only patients with data available were included.

Results

Patient Accountability

A total of 70 patients were enrolled into the study and included in the intent-to-treat population. One patient who was HBeAg negative before entering the study was excluded from the statistical analysis. Four patients had missing month 12 visit data and were treated as having no response in the intent-to-treat analysis of virological response. Seven patients withdrew before the end of the study, although three of these still returned for a follow-up assessment.

Table I. Baseline characteristics of the 70 patients with HBeAg positive chronic hepatitis B enrolled into the study

| | |
|--|----------------------|
| Age (y) | 30.6 (range 16–67.2) |
| Sex (% male) | 68.6 (48/70) |
| % of patients HBeAg positive | 98.6 (69/70) |
| % of patients HBeAb positive | 1.4 (1/70) |
| % of patients HBsAg positive | 100 (69/69) |
| % of patients HBV DNA positive | 100 (70/70) |
| ALT (U/L) | 50 (range 30–198) |
| Liver biopsy – severity of inflammation: % of patients with | |
| None | 2.0 (1/51) |
| Mild | 62.7 (32/51) |
| Moderate | 35.3 (18/51) |
| Severe | 0 |
| Disease stage (fibrosis): % of patients with | |
| None | 26.9 (14/52) |
| Mild | 55.8 (29/52) |
| Moderate | 9.6 (5/52) |
| Severe | 7.7 (4/52) |
| Cirrhosis | 0 |
| ALT = alanine aminotransferase; HBeAb = antibody to HBeAg; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus. | |

Three patients withdrew because of adverse events and four due to 'other' reasons. Results are presented for the intent-to-treat population.

Baseline Characteristics

The baseline characteristics of the 70 patients in the intent-to-treat population are shown in table I. Sixty-nine percent of patients were male (48/70), with a median age of 30.6 years (range 16–67.2 years). At baseline 69/70 (98.6%) were HBeAg positive and 69/70 (98.6%) were HBeAb negative (68/70 were both HBeAg positive and HBeAb negative). All patients with data recorded (69/69) were HBsAg positive and all patients were HBV DNA positive. Sixty-nine of 70 patients had ALT values available at baseline at which time 68 (99%) had values between 1.3 and 10 × ULN; the median baseline ALT value was 89 U/L (range 45–390 U/L). Seventy percent of patients (48/69) had previously received hepatitis B therapy, i.e. interferon- α , the standard therapy available at the time of the study, and were non-responders.

Liver biopsies showed that at baseline 32/51 patients (62.7%) had a mild severity grading of inflammation, 18/51 (35.3%) patients had moderate inflammation and no patients had severe inflammation. Twenty-nine patients of 52 (55.8%) had mild fibrosis (enlarged, fibrotic portal tracts), five patients (9.6%) had moderate fibrosis (periportal or portal-portal septa, but with intact architecture), four patients had severe fibrosis (architectural distortion), but no patients had cirrhosis.

Virological and Biochemical Response

In the intent-to-treat population, 19/69 (27.5%) of the patients who were HBeAg positive at baseline had a virological response, defined as loss of detectable HBeAg from serum with a reduction of HBV DNA to undetectable levels (table II). Twenty-two patients (31.9%) were HBeAg negative and 33 (47.1%) were HBV DNA negative. Figure 1 shows the mean serum ALT and AST values (U/L) throughout the treatment period. ALT values decreased steadily from a median baseline value of 89 U/L (range 45–390 U/L) to 27 U/L (6–550 U/L) by 12 months. At baseline, no patients had ALT values within the normal range, but this increased to 61.4% (43/70) of patients by 12 months. Similarly, median aspartate aminotransferase (AST) levels steadily decreased from a baseline value of 50 U/L (range

Table II. Virological and biochemical responses at 12 months in the intention-to-treat population^a

| Percentage of patients | |
|---------------------------------|----------------------------|
| HBeAg negative/HBV DNA negative | 27.5 (19/69 ^b) |
| HBeAg negative | 31.9 (22/69 ^b) |
| HBV DNA negative | 47.1 (33/70) |
| With HBeAg seroconversion | 27.9 (19/68 ^c) |
| HBsAg positive | 100 (69/69) |
| With normal ALT | 61.4 (43/70) |
| With normal AST | 74.3 (52/70) |

a For the virological responses, patients with missing month 12 data (n = 4) were treated as non-responders. For biochemical responses, patients with missing month 12 data (n = 10 for ALT and n = 13 for AST) were treated as non-responders.

b One patient was HBeAg negative at baseline.

c One patient was HBeAb positive at baseline.

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus.

30–198 U/L) to 24 U/L (range 10–300 U/L) at month 12, by which time 74.3% of patients (52/70) had values within the normal range.

Hepatitis B e Antigen and Hepatitis B Surface Antigen Seroconversion

Of the 70 patients in the intent-to-treat population, 68 were both HBeAg positive and HBeAb negative at baseline. Of these, 19 (27.9%) achieved

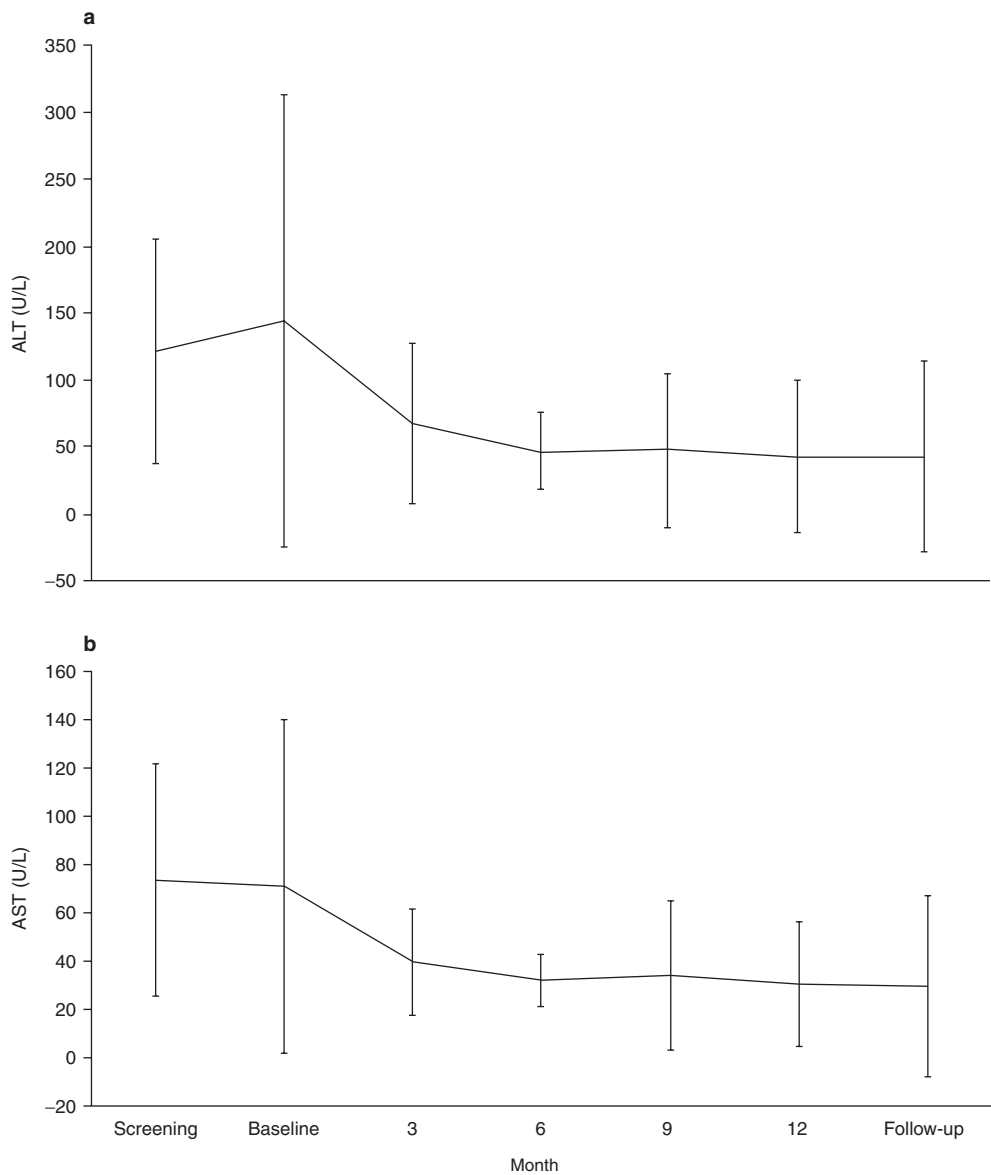


Fig. 1. Mean (a) alanine aminotransferase (ALT) and (b) aspartate aminotransferase (AST) levels (U/L) for hepatitis B patients during 12 months of treatment with lamivudine. Vertical lines represent mean \pm SD.

HBeAg seroconversion (HBeAg negative, HBeAb positive) by 12 months. One further patient was HBeAg negative with borderline HBeAb by 12 months and another patient was HBeAg negative/HBeAb negative. Of the two patients who were not HBeAg positive/HBeAb negative at baseline, one was positive for both at baseline and lost HBeAg by month 12 and the other was negative for both and gained HBeAg by month 12. No patients lost HBsAg during the study.

Safety

The mean duration of treatment was 365 ± 20 days, and the drug was well tolerated during this treatment period. The overall incidence of adverse events was 40% (28/70). Only five patients (7.1%) experienced a serious adverse event, of which three led to study withdrawal. The serious events were pregnancy, intracranial haemorrhage, dermatitis, abdominal pain and elevated creatinine phosphokinase; the latter two events were considered by the investigator to be attributable to lamivudine treatment. In total, ten patients (14.3%) experienced adverse events considered by the investigator to be drug-related. Table III shows the proportion of patients experiencing the most common adverse events ($\geq 5\%$); these were abdominal discomfort and pain, headaches, malaise/fatigue, viral respiratory infections and hair loss/alopecia.

ALT values $>10 \times$ ULN were noted in five patients (7%) at month 2 and then in one patient at month 8 (1%) and one patient at month 12 (2%).

Discussion

In chronic HBV carriers, only 1–2% will lose HBsAg per year, thus many remain infected for their

lifetime.^[14] These individuals have a greatly increased risk of severe liver disease and death from cirrhosis or primary hepatocellular carcinoma; one retrospective analysis of chronic HBV infection indicated that 40% of adult Asian men with this disease will die of either cirrhosis or hepatocellular carcinoma.^[9]

Patients with CHB who achieve HBeAg or HBsAg seroconversion typically maintain states of reduced HBV replication (or HBV elimination) for prolonged periods, often for life, and are thought to be at reduced risk for subsequent progression of their liver disease.^[15–21] This is thought to be true for both spontaneous and treatment-induced HBeAg seroconversions. Treatment with interferon- α can produce HBeAg seroconversion in approximately 20–40% of treated patients.^[21–23] However, patients who have high levels of serum HBV DNA or minimal evidence of inflammatory response (e.g. low serum ALT levels) appear to have lower response rates to interferon therapy.^[23] Furthermore, interferon use in patients with advanced liver disease requires particular caution.^[24–26] Hence, although interferon has been an important first step in hepatitis B therapy, widespread clinical acceptance of interferon treatment has been limited by its inconvenience (parenteral dosing), side effect profile, costs and lack of response in the majority of patients.

Lamivudine is the first oral antiviral therapy approved for the treatment of CHB. It is a nucleoside analogue that rapidly and profoundly suppresses HBV replication through inhibition of viral DNA synthesis. The efficacy and safety of lamivudine in CHB has been extensively studied in the Far East, the US and Europe and shows that lamivudine provides a rapid and consistent suppression of serum HBV levels with normalisation of ALT.^[10,11,27,28] Through its viral inhibition, lamivudine treatment results in enhanced seroconversion and reduced hepatic necroinflammatory activity and therefore appears to slow the progression of fibrosis in patients with ongoing viral replication and compensated liver disease.^[10–13]

Newer pharmacotherapeutic agents are being developed and hold promise for the treatment of HBV

Table III. Proportion of patients experiencing the most common adverse events ($\geq 5\%$)

| Adverse event | No. of patients with adverse events (%) |
|-------------------------------|---|
| Abdominal discomfort and pain | 4 (5.7) |
| Headaches | 4 (5.7) |
| Malaise and fatigue | 4 (5.7) |
| Viral respiratory infections | 5 (7.1) |
| Hair loss and alopecia | 4 (5.7) |

precore/core mutant.^[29] Adefovir dipivoxil is a recently approved nucleotide analogue for the treatment of chronic hepatitis B infection.^[30,31]

Conclusion

In this study of 70 Portuguese patients, HBV DNA responses to lamivudine therapy were similar to those reported elsewhere, with 47% (33/70) of patients having suppression of HBV DNA to undetectable levels after 52 weeks of lamivudine therapy. Improvements in ALT were also observed, with median values approaching the normal range after 6 months. Sixty-one percent of patients had ALT values within the normal range after 52 weeks of therapy, reflecting rates reported in other studies.^[10] Such normalisation of serum ALT is indicative of reduced liver damage, since serum ALT concentrations are thought to correlate reasonably well with liver disease measured histologically.^[32]

HBeAg seroconversion is a desirable goal in the treatment of CHB since it is recognised as being associated with a durable suppression of HBV replication with an improved clinical prognosis.^[33] In this study, after 52 weeks of lamivudine therapy HBeAg seroconversion (loss of detectable HBeAg and the appearance of anti-HBe) occurred in 27.9% (19/68) of patients. This is in agreement with other placebo-controlled lamivudine studies conducted elsewhere, reporting that 17–21% had seroconversion after 1 year.^[10,11,27] Most patients who had loss of HBeAg also had lost detectable HBV DNA, suggesting that HBeAg loss is associated with a marked suppression of HBV replication. The rate of HBeAg loss was higher than the rate of HBeAg seroconversion, although the difference was not as great as that reported in some studies.^[11,27] The rate of HBeAg loss was similar to that reported in a meta-analysis of interferon therapy (33%).^[21]

Lamivudine has an excellent, well-established safety and tolerability profile in patients with HBeAg positive CHB, with evidence to show that this tolerability is maintained with extended treatment for up to 4 years.^[10,28,34,35] In previous clinical trials the incidence of adverse events in lamivudine- or placebo-treated patients was similar during 1 year

of therapy, where most were mild and not considered to be related to lamivudine.^[10-12,27,28] Analyses of the subset of adverse events considered to be possibly or probably related to the study drug or of unknown relationship revealed similar frequencies of such events for patients treated with lamivudine or placebo. The incidence of adverse events in this Portuguese study was in keeping with these findings and revealed a similar profile of most commonly reported adverse events.

In conclusion, this Portuguese study corroborated the findings of earlier studies, showing that lamivudine treatment in patients with HBeAg positive CHB is well tolerated and results in both virological and biochemical improvements, with HBeAg seroconversion achieved in one third of patients.

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